

# FEMALE EXTRAPULMONARY GENITAL TUBERCULOSIS: FULL-TERM DELIVERIES AFTER 4 YEARS OF FOLLOW-UP

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Tuberculosis represents a long-standing and significant public health problem. Its clinical features and infectivity were recognized as long as 1,000 years ago [1]. Genital tuberculosis was first described by Morgani in the mid-eighteenth century, and the characteristics of the tubercle were reported by Koch in 1882 [2], more than 100 years after Morgani's initial description.

*Mycobacterium tuberculosis* infects 1.7 billion people or one-third of the world's population worldwide, and causes 3 million deaths each year, making it the most deadly individual infectious disease [3]. The annual incidence of tuberculosis in Taiwan is currently about 15,000 patients, including 5,000 infectious cases. Although the overall incidence of pulmonary tuberculosis has been decreasing, the number of new cases reported increased by as much as 36% in the United States during the years 1970–1974 [2]. It is relatively uncommon in developed countries, but it is still remarkable that the annual decline in the rate of extrapulmonary tuberculosis is much slower than that of pulmonary tuberculosis, especially in some racial groups, migratory minorities, and human immunodeficiency virus (HIV)-infected populations [4].

Female genital tuberculosis is the most destructive condition among the extrapulmonary tuberculous diseases in both developed and underdeveloped countries. A report published in 1972 showed that the incidence of tuberculosis was 4.8% in indigent pregnant women in New Orleans, Louisiana, in the United States [5].

Female patients may frequently present with infertility, menstrual disturbance, fever, anorexia, abdominal fullness or pain. Infertility is the most bothersome of these and may cause complications for young couples [6–8]. However, it is regrettable that the diagnosis is often delayed until histopathologic results reveal the typical findings of tuberculous granulomas.

A 24 year-old, gravida 0, para 0, woman was admitted to our hospital with a 1-week history of epigastric and abdominal fullness and pain. She denied fever, anorexia or weight loss. Her menstrual cycles were regular and stool passage was smooth. She was ethnically Chinese, had been raised in Burma, and had been living as a housewife in Taipei for 3 years prior to her admission. She was not using any contraception. Her tuberculosis screening on arrival was negative, and there was no relevant medical or surgical history, and no family history of tuberculosis. She denied ever having had tuberculosis or being in contact with any tuberculosis patients. General physical examination results were unremarkable except for a soft and distended abdomen with mild to moderate tenderness. The chest X-ray results were normal. Abdominal sonography revealed profuse ascites. Paracentesis showed an increased white cell count and mononuclear population, gram-negative strain, no acid-fast bacilli, and negative results for malignant cells. The only increased tumor marker was CA-125 at 600 U/mL. Laparoscopy finally identified 2,100 mL of yellowish turbid ascitic fluid and widespread miliary deposits all over the abdominal, pelvic and parietal peritoneum, extending up to the subphrenic dome. The uterus, bilateral fallopian tubes and ovaries (Figure 1) were edematous, slightly enlarged and covered with miliary mini-tubercles (Figure 1). Examination of frozen sections and final histopathologic results of a pelvic serosal biopsy revealed chronic granulomatous inflammation characteristic of tuberculosis. Endometrial

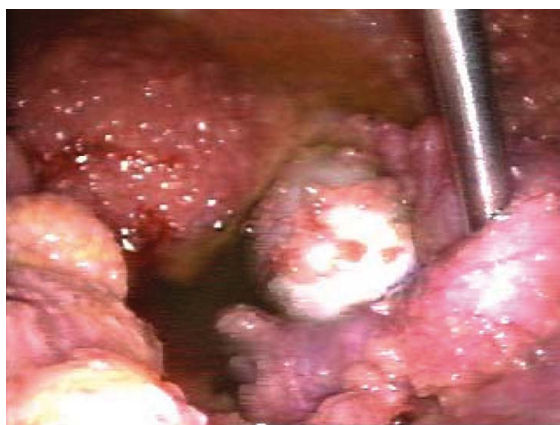


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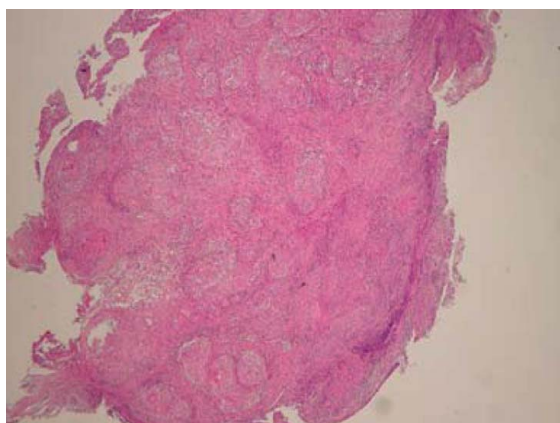
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**Figure 1.** Both fallopian tubes and ovaries were edematous and obviously covered with miliary mini-tubercles.



**Figure 2.** The soft tissue from the serosal surface of the uterus showed chronic caseating granulomatous inflammation, composed of areas of caseous necrosis surrounded by fibroblast proliferation, epithelioid histiocytes, Langerhans giant cells and round cell infiltration (hematoxylin and eosin, 40×).

curettage showed tuberculous endometritis with granulomatous tubercles (Figure 2). Subsequent laboratory investigations, including acid-fast stain and culture of ascites, pleural effusion, sputum and mid-stream urine, all produced negative findings. After laparoscopy, triple therapy with isoniazid (100 mg), rifampicin (150 mg) and ethambutol (400 mg), three tablets per day of each, was started and continued for 18 months. Oral prednisolone 30 mg/day in three doses was also prescribed for the first 3 months. Pelvic sonographic abnormalities and elevated CA-125 levels both recovered after 4 months of antituberculous treatment.

The patient received a full course of medication and regular follow-up at our gynecologic and chest outpatient units for 18 months until February 2005. The patient became pregnant 10 months after completion of the treatment at the end of 2005, and delivered a full-term baby by vaginal delivery. She gave birth to a second child at the end of 2007. Both pregnancy

courses, including fetal morphology and physiology, were normal.

Many medical references and case reports have indicated that pelvic tuberculosis remains a cause of female infertility, despite a decline in the incidence of tuberculosis during recent years. The chances of successful pregnancy after medical and surgical treatment are generally poor, with most pregnancies resulting in ectopic pregnancies or abortions [9–11]. Some studies found that *in vitro* fertilization and embryo transfer could offer the chance of a successful pregnancy outcome in affected women [12]. In this report, we present a nulliparous woman with genital tuberculosis treated with triple antituberculous chemotherapeutic agents from July 2003 through to January 2005.

There are few available prospective data regarding the optimal management of genital tuberculosis. The guidelines recommend 6 months of treatment, with the inclusion of pyrazinamide for the first 2 months of treatment, providing that the organism is susceptible [13,14]. The present patient had a successful outcome after 18 months of triple therapy with isoniazid, rifampicin and ethambutol, combined with a short period of oral prednisolone, following a surgical diagnosis. This case also emphasizes the importance of an early diagnosis, immediate and adequate treatment and patient compliance.

Female genital tuberculosis usually begins with a hematogenous focus in the endosalpinx, from which it may spread to the endometrium (50%), ovaries (30%), cervix (5–15%) and vagina (1%) [3]. The most common complaint is infertility. Symptoms, when present, are usually local and consist of lower abdominal pain or menstrual disorders. The clinical pictures may include pelvic inflammatory disease unresponsive to conventional therapy. A granulomatous exophytic or ulcerating mass resembling carcinoma may be present in the cervix [13]. Systemic symptoms are uncommon, and evidence of old tuberculosis need not be present. Cultures of menstrual blood or endometrial scrapings may be positive for tuberculosis, as in the present case. Ectopic pregnancies are common when pregnancies occur in the presence of pelvic tuberculosis. The diagnosis is usually made on the basis of examination of tissue removed at surgical intervention or investigation, although a definite diagnosis is only possible through isolation of *M. tuberculosis* from the genital tract. The histopathologic demonstration of granuloma is generally accepted as a major criterion, since nontuberculous granulomas are extremely rare [4].

Treatment with chemotherapeutic agents is generally effective. However, indications for surgery include: (1) persistence or progression of the disease despite adequate medical treatment; (2) suggested residual

large tubo-ovarian abscess; (3) positive endometrial culture/histology and recurrence of pain or bleeding after 9 months of medical treatment; and (4) fistulas that fail to heal [13]. Surgical therapy usually consists of total abdominal hysterectomy and bilateral salpingo-oophorectomy. Surgery should be performed at least 6 weeks after initiation of antituberculous therapy, because antimicrobial treatment facilitates the surgical procedure and reduces the risk of perioperative complications [5]. Infertility clinics should also test to exclude the possibility of tuberculous infection [15,16].

In the light of recent low birth rates and the high proportion of pregnant immigrant women in Taiwan, it is important to identify pregnant women who are infected with tuberculosis because of the risk of developing an active disease that could be transmitted to their newborn babies. Tuberculin skin tests and chest roentgenography are the complementary screening methods used. There have been no reports of adverse effects in pregnant women or their babies as a result of tuberculin testing; however, chest X-rays should be avoided during the first trimester. Priority candidates for tuberculin testing among pregnant women include: (1) women with any signs or symptoms suggestive of tuberculosis; (2) those with known or suggested exposure to tuberculosis; (3) women with any risks factors for tuberculosis such as diabetes or HIV infection; (4) women employed in hospitals, nursing homes or prisons; and (5) all women from socioeconomic or demographic groups with a high prevalence of tuberculosis [17]. The impact of pregnancy on tuberculosis appears to be minimal, except for potentially obscuring its diagnosis and possibly increasing the risk of tuberculosis activation during the postpartum period. Because a substantial proportion of pregnant tuberculous women are asymptomatic, diagnosis should emphasize a careful history, epidemiologic investigation of case contacts, and routine questioning of pregnant women in high-risk groups or from endemic areas. Furthermore, mothers can still breast-feed while being treated with antituberculous drugs. Transfer of the drugs to infants can be reduced as much as possible via the modified feeding method, which involves giving the mother her medication after feeding, and substituting a bottle for the next feed [5].

The decline in extrapulmonary tuberculosis has been relatively small over the last few years, and future trends will reflect the impact of the HIV epidemic, which has been shown to promote the progression from latent subclinical tuberculosis infection to overt clinical tuberculosis [4]. The proportion of cases of extrapulmonary tuberculosis in patients with acquired immunodeficiency syndrome is much higher than in patients without the syndrome [18]. Thus, the impact of shifting

demographics on extrapulmonary cases will also require assessment of the impact of HIV infection on extrapulmonary tuberculosis.

Female extrapulmonary genital tuberculosis is rare in developed countries. However, the increase in immigrants, foreigners, infertile couples and HIV-infected female patients in Taiwan means that more attention should be paid to this condition, especially in infertility clinics, large hospitals and medical centers [19]. It should be kept in mind as a differential diagnosis in patients who present with the common symptoms of abdominal or pelvic pain or fullness, menstrual abnormalities or infertility, especially in those susceptible patient populations described above. We recommend that all patients having a positive tuberculin test combined with either menstrual disorders or complaints of infertility should undergo aggressive evaluation of the genital tract for possible extrapulmonary tuberculosis. Early diagnosis and treatment are paramount to preserve fertility and reduce other complications, as demonstrated by the present case.

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